

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 9/36</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/30692</b> <b>(43) International Publication Date:</b> 24 June 1999 (24.06.99)
<b>(21) International Application Number:</b> PCT/US98/25766 <b>(22) International Filing Date:</b> 4 December 1998 (04.12.98) <b>(30) Priority Data:</b> 08/989,253 12 December 1997 (12.12.97) US <b>(71) Applicant:</b> ANDRX PHARMACEUTICALS, INC. [US/US]; Suite 201, 4001 S.W. 47th Avenue, Fort Lauderdale, FL 33314 (US). <b>(72) Inventors:</b> CHEN, Chih-Ming; 10680 S.W. 40th Manor, Davie, FL 33328 (US). CHOU, Joseph; 5755 N.W. 54th Place, Coral Springs, FL 33067 (US). WONG, David; Apartment 214, 555 South Luna Court, Hollywood, FL 33081 (US). <b>(74) Agent:</b> COSTIGAN, James, V.; Hedman, Gibson & Costigan, P.C., 1185 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> IMPROVED HMG CoA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION <b>(57) Abstract</b> <p>A controlled release dosage formulation is described which is based on a combination of: (a) a compressed tablet core which contains an alkyl ester of a hydroxy substituted naphthalene derivative, a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and (b) an outer coating layer which completely covers the osmotic core and comprises a pH sensitive coating agent and a water insoluble polymer.</p> <p>103 (102(a) date)</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

CoA  
IMPROVED HMG ~~CO~~ REDUCTASE INHIBITOR EXTENDED RELEASE  
FORMULATION

5

BACKGROUND OF THE INVENTION

10       The use of HMG-CoA reductase inhibitors for the  
reduction of serum cholesterol levels is well know.  
These compounds include alkyl esters of hydroxy  
substituted naphthalenes which are orally effective in  
the reduction of serum cholesterol levels. Examples of  
these compounds include mevastatin which is described  
15       in U.S. 3,671,523; lovastatin which is described in  
U.S. 4,231,938; pravastatin which is described in U.S.  
4,346,227; and simvastatin which is described in  
U.S. 4,444,784. All of these patents are incorporated by  
reference.

20       Lovastatin is a metabolite which is produced by  
the natural fermentation of an fungus of the  
Aspergillus genus. Lovastatin acts systemically to  
lower blood serum cholesterol levels by disrupting the  
biosynthesis of cholesterol in the liver, where 70% to  
25       80% of body cholesterol is produced. Specifically  
lovastatin interrupts a step in the endogenous  
production of cholesterol by inhibiting the HMG  
coenzyme A reductase from combining with bile acids in  
the digestive tract such that the bile acids are  
30       excreted from the body without reabsorption. With  
synthesis in the liver thusly inhibited, the liver  
cells must take cholesterol from the bloodstream, and  
they do so by increasing their production of cell  
surface receptors for LDL cholesterol. Lovastatin  
35       formulations are generally capable of lowering the  
blood serum cholesterol level by about 30-40%. The  
other compounds of this class are derived from natural

or synthetic sources using well known procedures and have similar mechanisms of activity.

5           However, it is desirable to enhance the activity of these compounds to achieve even greater reductions of blood serum cholesterol levels in connection with the treatment of hypercholesterolemia and other maladies. Accordingly, the present invention provides a novel controlled release formulation of a compound which is an alkyl ester of a hydroxy substituted naphthalene derivative which provides for a gradual  
10           release of the compound. This formulation has been prepared to provide a slow controlled release of these compounds in order to provide a more constant level of bioavailability in order to provide an enhanced effect that cannot be achieved by conventional immediate  
15           release dosing. The use of a controlled release form of is believed to be specially useful for those who have meals at irregular times or those who frequently eat snacks between meals. These subjects include night  
20           shift workers, airline personnel and travelers, and those individuals with blood sugar problems who eat frequent small meals. In addition, it is believed that the human body synthesizes high amounts of cholesterol during the hours of sleep and it is desirable in  
25           certain cases to provide therapeutic level of these compounds during periods of sleep.

          Controlled release formulations have been described in U.S. 4,615,698 which have been based on an osmotic dosage form which is designed to collapse and  
30           cause the faced surfaces to come into a close contacting arrangement as the drug is delivered through a passageway in the semi-permeable wall of the dosage form. In addition, U.S. 4,503,030 discloses an osmotic dosage form which has a passageway and a semi-permeable  
35           membrane consisting of a particular cellulose polymer and a pH sensitive material which could be an enteric coating material. This patent describes the use of 1:1

mixtures of a pH sensitive material and cellulose polymer which are applied at a level of about 7% by weight based on the total weight of the osmotic core tablet and coating material.

5           The applicants have discovered that a ratio of 0.75:1, and lower, of pH sensitive material to cellulose polymer may be used to provide a stable membrane around an osmotic core tablet at a coating level of 1-4% by weight based on the total weight of  
10 the osmotic core tablet and coating material. These osmotic tablets will substantially, completely deliver the compound without the need to provide a passageway in the tablet according to the teachings of the prior art. In addition the osmotic tablet of the invention  
15 will provide higher bioavailability and lower peak plasma drug concentrations than are provided by the same weight of the alkyl ester of a hydroxy substituted naphthalene derivative in a conventional immediate release dosage form.

20

#### SUMMARY OF THE INVENTION

The present invention provides a controlled release lovastatin dosage formulation which comprises:  
25 (a) a compressed tablet core which contains an alkyl ester of a hydroxy substituted naphthalene derivative, a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and  
(b) an outer coating layer which completely covers the  
30 osmotic core and comprises a pH sensitive coating agent and a water insoluble polymer.

An optional sealing coat may be applied to the compressed tablet core and an optional coating layer comprising an enteric coating agent may be applied  
35 under the outer coating layer as an inner coating or as an overcoat over the outer coating layer. The tablet core may be compressed using a smooth faced tablet die.

The preferred alkyl ester of a hydroxy substituted naphthalene compound is lovastatin.

Accordingly, it is a primary object of the present invention to provide a controlled release form of an alkyl ester of a hydroxy substituted naphthalene derivative.

It is also an object of the present invention to provide a controlled release dosage formulation of an alkyl ester of a hydroxy substituted naphthalene derivative which substantially completely releases said alkyl ester in about 4 to 30 hours in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C. and 50rpm.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG.1 is a graph of in vitro dissolution data which shows the dissolution profile of the formulation of Example 1 in 2% sodium lauryl sulfate at pH 7.0 in  $\text{NaH}_2\text{PO}_4$  buffer in a USP XXII Type II dissolution apparatus at 50 rpm at 37°C.

FIG. 2 is a graph of comparative data which shows the in vivo effect of a conventional immediate release dose of 40mg of lovastatin and the in vivo effect of a extended release dose, according to the invention, of 40mg of lovastatin.

FIG.3 is a graph of in vitro dissolution data which shows the dissolution profiles of the formulations of Examples 2, 3 and 4 in 2% sodium lauryl sulfate at pH 7.0 in  $\text{NaH}_2\text{PO}_4$  buffer in a USP XXII Type II dissolution apparatus at 50 rpm at 37°C.

#### DETAILED DESCRIPTION OF THE INVENTION

The controlled release dosage form is preferably prepared by combining mevastatin, pravastatin, simvastatin or lovastatin with a pharmaceutically

acceptable, water swellable polymer and an osmotic agent into a compressed tablet core having an optional first coating for sealing and protection and a second coating comprising a pH sensitive agent water insoluble polymer. Mevastatin, pravastatin, simvastatin and lovastatin are well known compounds that are described in the prior art including the particular patents which have been cited herein. It is also within the scope of the invention to use mixtures of different alkyl esters of hydroxy substituted naphthalenes.

Specifically, a pharmaceutically acceptable, water swellable polymer and an osmotic agent are combined with the drug which may be micronized or unmicronized or amorphous or crystalline and compressed to form the tablet core. The osmotic agent is any non-toxic pharmaceutically acceptable water soluble compound which will dissolve sufficiently in water and increase the osmotic pressure inside the core of the tablet. The osmotic agents include the simple sugars and salts such as sodium chloride, potassium chloride, magnesium sulfate, magnesium sulfate, magnesium chloride, sodium sulfate, lithium sulfate, urea, inositol, sucrose, lactose, glucose, sorbitol, fructose, mannitol, dextrose, magnesium succinate, potassium acid phosphate and the like. The preferred osmotic agent for the tablet core is a simple sugar such as anhydrous lactose in the range of 0-50% by weight, based on the weight of the compressed, uncoated tablet.

The pharmaceutically acceptable, water swellable polymer may be any pharmaceutically acceptable polymer which swells and expands in the presence of water to slowly release the lovastatin. These polymers include polyethylene oxide, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and the like. In a preferred embodiment, the water swellable polymer will be polyethylene oxide (obtained

from Union Carbide Corporation under the trade name Polyox WSR Coagulant or Polyox WSR N 80). These materials form a viscous gel in water or other solvent system at a sufficient concentration to control the release of the lovastatin. This will generally require a concentration of the pharmaceutically acceptable, water swellable polymer of about 0-50% by weight of the compressed, uncoated tablet.

Binder may be employed in a sufficient amount so that when it is combined with a suitable solvent, mixed with the water soluble osmotic agent and agitated, granules will be formed which may be compressed into a tablet core. Prior to compressing the granules, the conventional solid pharmaceutical diluents such as microcrystalline cellulose, lactose, dextrose and the like may be added to the granule forming mixture in amounts from about 0 to 51% weight based on the weight of the compressed, uncoated tablet. In the present case, the above mentioned osmotic agent, lactose, may function as a binder in the tablet compression step.

In the preparation of the tablets of the invention, various solvents may be used to prepare the granules. In addition, various other diluents, excipients, lubricants, dyes, pigments, dispersants, emulsifiers, etc. may be used to optimize the formulations of the invention.

Additionally, a surfactant is used in the preferred embodiment. The surfactant may be any ionic or non-ionic water soluble surfactant which may be employed in the range of 0-50% by weight or preferably 1-5% by weight. The preferred surfactant for the present formulation is sodium lauryl sulfate but other surfactants such as polysorbate 20, 60 or 80; polyoxl 40 stearate and the like.

Furthermore, the preferred embodiment may comprise a lubricant. Ideally, the lubricant will be



in the range of 0.5 to 2.5% by weight of the compressed, uncoated tablet.

After the above described tablet core is formed, it is coated with: 1) an optional protective first coating on the tablet core and/or an optional pH sensitive coating; 2) an outer coating comprising a pH sensitive agent and a water insoluble polymer.

Specifically, a protective first coating may be used at a level in the range of 0-10% by weight which may be applied from a coating system such as Opadry Clear sold by Colorcon Corporation. In an especially preferred embodiment, the Opadry Clear will be 2.83% by weight and will be combined with an osmotic agent in the range of 0-10% by weight. While the osmotic agent may be any salt, low molecular weight molecule or water soluble polymers, the preferred agent is sodium chloride. The osmotic agent is added to the coating system when the coating system is being dispersed into purified water. The coating system which contains the osmotic agent may then be sprayed onto the tablets to form a protective coating layer. As mentioned above, this protective first coating is optional.

An optional inner or over coat over the outer coat may also be applied which comprises a pH sensitive polymer which functions as an enteric polymer in that it does not begin to dissolve until pH conditions in excess of the stomach region are encountered. Generally, the pH sensitive materials do not dissolve and begin to release the active drug until a pH above 3.0 and preferably above 5.5. Materials such as such as Eudragit L (copolymer of poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit S (copolymer of poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B). hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate and the like may be used in

the range of 0-30% by weight and preferably 2 to 4 percent by weight of the combined weight of the compressed, uncoated tablet and the inner coating of the pH sensitive polymer.

5           The outer coating comprises a pH sensitive polymer which functions as an enteric polymer in that it does not begin to dissolve until pH conditions in excess of the pH of the stomach region are encountered and a water insoluble polymer which provide controlled  
10       release properties to the coating formulation. The pH sensitive polymer is the same type of material that is described above as the optional inner coating layer. The water insoluble polymer may be a cellulosic polymer such as ethylcellulose, cellulose acylate, cellulose  
15       mono-, di- or triacetate. The pH sensitive polymer and the insoluble cellulosic polymer are used at a weight ratio of about 0.1:1 to 0.75:1, preferably 0.25:1 to 0.5:1 of pH sensitive polymer to water insoluble  
20       cellulosic polymer. A combined coating weight of about 0.5-5% by weight and preferably 1 to 4% by weight and especially preferred is 1 to 3% by weight of the gained weight based on the weight of the coated tablet core. Cellulose acetate is the preferred water insoluble polymer and the outer coating is preferably applied as  
25       a suspension in acetone.

          Furthermore, a plasticizer or combination of plasticizers may be added to the inner, outer or over coating to provide elasticity and shape to the coating. While the plasticizer or combination of plasticizers  
30       may be any water soluble or water insoluble formulation in the range of 0-10% by weight and preferably 0.5 to 5% by weight of the outer coating composition. Acetyltributyl citrate is the preferred plasticizer but materials such as acetyl triethyl citrate, dibutyl  
35       phthalate, triacetin, diethyl phthalate, polyethylene glycol, propylene glycol and the like may be utilized.

          An antioxidant such as BHA or BHT may be added

to the tablet core as a stabilizer at a level of 0.001 to 0.01% by weight of the tablet core.

5 Lastly, a channelling agent is mixed with the  
aforementioned components of the outer coating. A  
channelling agent may be employed to increase the  
porosity of the film coating in order to increase the  
amount of the fluids that penetrate the tablet core and  
increase the rate of hydration. This allows the release  
of the lovastatin after the outer film coat ruptures.  
10 Generally, channelling agents may be any salts,  
surfactants, or short-chain water soluble polymers in  
a water channel forming effective amount i.e. 1 to 5%  
by weight, based on the total weight of the core and  
all coating components. The channeling agents include  
15 any pharmaceutically acceptable water soluble salt,  
surfactant, or short chain water soluble polymer such  
as sodium chloride, potassium chloride, sucrose,  
polysorbate-80, hydroxypropyl cellulose, hydroxyethyl  
cellulose and the like.

20 Also, the preferred embodiment of the inner or  
over coating is supplied with an anti-sticking agent  
such as talc to overcome any tablet to tablet  
stickiness during the coating process. The amount of  
anti-sticking agent is an amount which prevents  
25 sticking which may be in the range of 0-6% by weight  
based on the weight of the tablets and the coating  
materials on a dry weight basis.

Although the applicants do not wish to be bound  
by any theory by which the invention operates, it is  
30 believed that the tablets of the invention release the  
lovastatin by osmotic pressure. Water is drawn into the  
tablet and it expands to the point where the outer  
coating fails in one particular area to form a  
constricted opening which releases the internal  
35 contents of the tablet which contain the drug.  
Thereafter, the aqueous medium of the tablet shell will  
continue to release the drug as it dissolves until the

osmotic pressure inside the tablet shell equals that of the surrounding environment. At the late stages of the in vivo release of lovastatin, it is believed that the tablet shell will collapse and/or disintegrate completely to substantially completely release the remaining drug. The water insoluble coating is not absorbed in the gastrointestinal tract and is eliminated in the feces.

The tablets of the invention may be made in a smooth faced tablet die. Thereafter the tablet is provided with the outer coating which, because of surface tension, will result in a thinner coating layer over the corners of the tablet which will provide an area in the outer coating which will form a channel to allow intestinal fluid to reach the core of the tablet.

The tablets of the invention will have the following general formula:

	INGREDIENTS	POSSIBLE RANGE, wt%
	<u>Tablet Core</u>	
5	Alkyl ester of a substituted naphthalene	3-20
	Water Swellable Polymer	10-40
	Antioxidant	0.001-0.01
	Osmotic Agents	20-80
	Surfactant	0-5
10	Lubricant	0-5
	<u>Coatings:</u>	
	Seal Coating	0-10
	Osmotic Agents	0-10
15	<u>Inner Coating</u>	
	Enteric Polymer	0-30
	Anti-sticking Agent	0-6
	Plasticizer	0-6
20	Channelling Agents	0-6
	<u>Outer Coating</u>	
	Blend of Enteric Polymer and Water-insoluble Polymer	0.5-5
25	Plasticizer(s)	0-1
	Channelling Agents	0.2.5
	<u>Overcoat</u>	
	Enteric Polymer	0-30
30	Anti-sticking Agent	0-6
	Plasticizer	0-6
	Channelling Agents	0-6
35	<b>TOTAL</b>	100

DESCRIPTION OF THE PREFERRED EMBODIMENTS

## EXAMPLE 1

A tablet having the following formula was prepared:

	lovastatin	11.99wt%	40.0mg
5	Polyox WSR Coagulant, NF*	4.50wt%	15.0mg
	Polyox WSR N 80, NF**	17.98wt%	60.0mg
	lactose (anhydrous)	50.65wt%	169.0mg
	sodium lauryl sulfate	3.00wt%	10.0mg
	silicon dioxide Fumed USP/NF	0.45wt%	1.5mg
10	Myvaplex 600P***	1.80wt%	6.0mg

\* polyethylene oxide Mw No av 5,000,000

\*\* polyethylene oxide Mw No av 200,000

\*\*\* glyceryl monostearate

15 Seal Coating:

	Opadry Clear****	2.81wt%	9.4mg
	sodium chloride	0.93wt%	3.1mg

20 \*\*\*\* mixture containing hydroxypropyl methyl cellulose and polyethylene glycol

Inner Coating:

	hydroxypropylmethylcell. phthal.55	2.27wt%	7.58mg
	talc	0.78wt%	2.6mg
25	acetyl tributyl citrate	0.22wt%	0.75mg
	sugar, confectioners 6X micronized	0.62wt%	2.08mg

Outer Coating:

	cellulose acetate	1.00wt%	3.32mg
	Eudragit S 100 <sup>1</sup>	0.34wt%	1.13mg
30	triacetin	0.08wt%	0.27mg
	polyethylene glycol 400	0.08wt%	0.27mg
	sugar, confectioners 6X micronized	<u>0.50wt%</u>	1.66mg

100.0wt% 333.66mg

35 <sup>1</sup> Eudragit S 100 (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B)

The following describes the process of making the

above described dosage form:

STEP 1, THE TABLET CORE

(a) Granulation

- 5 1. Pass Polyox WSR N80, sodium lauryl sulfate and anhydrous lactose through a 30 mesh stainless steel screen.
2. Charge the screened materials and lovastatin (micronized) into a vertical granulator.
- 10 3. Dissolve butylated hydroxy anisole in ethanol.
4. Mix ethanol, and purified water.
5. Pre-mix the powder mixture for 5 minutes.
6. Blend the powder mixture again, add the butylated hydroxyanisole solution and then the ethanol/water
- 15 mixture.
7. Dry the granules at 45-50°C until the moisture content is lower than 1.8wt%.
8. Pass the granules through a 1575 mesh using a Comil.

20 Tabletting

1. Mix Cab-O-Sil and Polyox WSR N80.
2. Pass the mixture of Cab-O-Sil and Polyox WSR N80 through a 24 mesh stainless steel screen with the
- 25 Polyox WSR Coagulant.
3. Blend the screen materials with lovastatin granules for 15 minutes.
4. Pass Myvaplex through a 30 mesh stainless steel screen and combine with the other screen materials.
- 30 5. Blend for five minutes.
6. Compress the blend into tablets (300mg, round, standard concave, 11/32") which contain 40mg of lovastatin.

35 Seal Coating: Opadry Clear

1. Dissolve sodium chloride in purified water.
2. Disperse Opadry Clear into the sodium chloride

solution.

3. Spray lovastatin tablets with the aqueous coating suspension using a coater.

5 Inner Coating: Hydroxypropyl methylcellulose phthalate  
55

1. Dissolve hydroxypropyl methylcellulose phthalate 55 in acetone using a homogenizer.

10 2. Add acetyl tributyl citrate to the acetone solution and mix it with a homogenizer until a homogenized dispersion is obtained.

3. Add talc and sugar to the solution and mix it with a homogenizer until a homogenized dispersion is obtained.

15 4. Replace the homogenizer with a magnetic mixer and stir the coating mixture throughout the coating process.

5. Spray the Opadry Clear coated lovastatin tablets with the coating dispersion in a coater.

20

Outer Coating: cellulose acetate

1. Dissolve cellulose acetate and Eudragit S100 in acetone using a homogenizer.

25 2. Add polyethylene glycol 400, triacetin and sugar to the solution and mix until a homogeneous dispersion is obtained.

3. Spray the coating suspension onto the tablets in a coater.

30 Release in the above described manner will result in the dissolution profile shown in FIG. 1:

It is believed that administration of the above described micronized Lovastatin in these amounts will be particularly effective in inhibiting the biosynthesis of cholesterol in the liver through  
35 interruption of HMG coenzyme A reductase. The dosage of lovastatin should be individualized depending on the desired and/or degree of serum cholesterol that is



desired. Generally 10 to 80mg of lovastatin per day should be administered by mouth depending on the response and the degree of reduction in serum cholesterol level that is indicated.

5

## EXAMPLE 2

A tablet having the following formula was prepared:

10	lovastatin	12.11wt%	40.0mg
	Polyox WSR Coagulant, NF*	4.54wt%	15.0mg
	Polyox WSR N 80, NF**	17.71wt%	58.5mg
	lactose (anhydrous)	51.13wt%	168.9mg
	sodium lauryl sulfate	3.03t%	10.0mg
15	silicon dioxide Fumed USP/NF	0.45wt%	1.5mg
	butylated hydroxy anisole	0.03wt%	0.10mg
	Myvaplex 600P***	1.82wt%	6.0mg
	* polyethylene oxide Mw No av 5,000,000		
	** polyethylene oxide Mw No av 200,000		
20	*** glyceryl monostearate		

## Seal Coating:

	Opadry Clear****	2.85wt%	9.4mg
	sodium chloride	0.94wt%	3.1mg
25	**** mixture containing hydroxypropyl methyl cellulose and polyethylene glycol		

## Inner Coating:

	hydroxypropylmethylcell. phthal.55	2.29wt%	7.58mg
30	talc	0.79wt%	2.6mg
	acetyl tributyl citrate	0.23wt%	0.75mg
	sugar, confectioners 6X micronized	0.08wt%	0.27mg

Outer Coating:

	cellulose acetate	1.00wt%	3.32mg
	Eudragit S 100 <sup>1</sup>	0.34wt%	1.13mg
5	triacetin	0.08wt%	0.27mg
	polyethylene glycol 400	0.08wt%	0.27mg
	sugar, confectioners 6X micronized	<u>0.50wt%</u>	1.66mg
		100.0wt%	330.35mg

10      1      Eudragit    S      100      (poly(methacrylic      acid,  
methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP  
Type B)

Coated tablets were prepared using the general procedure of Example 1.

15 EXAMPLE 3

A tablet having the following formula was prepared:

	lovastatin	12.14wt%	20.0mg
	Polyox WSR Coagulant, NF*	4.55wt%	7.5mg
	Polyox WSR N 80, NF**	17.76wt%	29.25mg
20	lactose (anhydrous)	51.30wt%	84.5mg
	sodium lauryl sulfate	3.04wt%	5.0mg
	silicon dioxide Fumed USP/NF	0.46wt%	0.75mg
	butylated hydroxy anisole	0.03wt%	0.05mg
	Myvaplex 600P***	1.82wt%	3.0mg
25	* polyethylene oxide Mw No av 5,000,000		
	** polyethylene oxide Mw No av 200,000		
	*** glyceryl monostearate		

Seal Coating:

30	Opadry Clear****	3.42wt%	5.63mg
	sodium chloride	1.14wt%	1.88mg
	**** mixture containing hydroxypropyl methyl cellulose and polyethylene glycol		

35 Outer Coating:

cellulose acetate	1.43wt%	2.36mg
Eudragit S 100 <sup>1</sup>	0.49wt%	0.80mg
triacetin	0.11wt%	0.19mg

polyethylene glycol 400	0.11wt%	0.19mg
sugar, confectioners 6X micronized	0.72wt%	1.18mg

## 5 Overcoat:

hydroxypropylmethylcell. phthal.55	0.77wt%	1.27mg
10 talc	0.30wt%	0.49mg
triacetin	0.12wt%	0.20mg
sugar, confectioners 6X micronized	0.30wt%	0.49mg
15	100.0wt%	146.73mg
1 Eudragit S 100 (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B)		

20 The following describes the process of making the above described dosage form:

## STEP 1, THE TABLET CORE

## (a) Granulation

- 25 1. Pass Polyox WSR N80, sodium lauryl sulfate and anhydrous lactose through a 30 mesh stainless steel screen.
2. Charge the screened materials and lovastatin (micronized) into a vertical granulator.
- 30 3. Dissolve butylated hydroxy anisole in ethanol.
4. Mix ethanol and purified water.
5. Pre-mix the powder mixture for 5 minutes.
6. Blend the powder mixture again, add the butylated hydroxyanisole solution and then the ethanol/water
- 35 mixture.
7. Dry the granules at 45-50°C until the moisture content is lower than 1.8wt%.
8. Pass the granules through a 1575 mesh using a Comil.

## 40 Tableting

1. Mix Cab-O-Sil and Polyox WSR N80.

2. Pass the mixture of Cab-O-Sil and Polyox WSR N80 through a 24 mesh stainless steel screen with the Polyox WSR Coagulant.
3. Blend the screen materials with lovastatin granules for 15 minutes.
4. Pass Myvaplex through a 30 mesh stainless steel screen and combine with the other screen materials.
5. Blend for five minutes.
6. Compress the blend into tablets (164.72mg, round, standard concave, 17/64" dia.) which contain 20mg of lovastatin.

Seal Coating: Opadry Clear

1. Dissolve sodium chloride in purified water.
2. Disperse Opadry Clear into the sodium chloride solution.
3. Spray lovastatin tablets with the aqueous coating suspension using a coater.

20 Inner Coating: None

Outer Coating: cellulose acetate

1. Dissolve cellulose acetate and Eudragit S100 in acetone using a homogenizer.
2. Add polyethylene glycol 400, triacetin and sugar to the solution and mix until a homogeneous dispersion is obtained.
3. Spray the coating suspension onto the tablets in a coater.

Overcoating: Hydroxypropyl methylcellulose phthalate 55

1. Dissolve hydroxypropyl methylcellulose phthalate 55 in acetone using a homogenizer.
2. Add acetyl tributyl citrate to the acetone solution and mix it with a homogenizer until a homogenized dispersion is obtained.
3. Add talc and sugar to the solution and mix it with a homogenizer until a homogenized dispersion is obtained.

4. Replace the homogenizer with a magnetic mixer and stir the coating mixture throughout the coating process.

5. Spray the Opadry Clear coated lovastatin tablets with the coating dispersion in a coater.

#### EXAMPLE 4

A tablet having the following formula was prepared:

	lovastatin	12.20wt%	20.0mg
10	Polyox WSR Coagulant, NF*	4.57wt%	7.5mg
	Polyox WSR N 80, NF**	17.84wt%	29.25mg
	lactose (anhydrous)	51.53wt%	84.5mg
	sodium lauryl sulfate	3.05wt%	5.0mg
	silicon dioxide Fumed USP/NF	0.46%	0.75mg
15	butylated hydroxy anisole	0.03wt%	0.05mg
	Myvaplex 600P***	1.83wt%	3.0mg

\* polyethylene oxide Mw No av 5,000,000

\*\* polyethylene oxide Mw No av 200,000

\*\*\* glyceryl monostearate

20

Seal Coating:

	Opadry Clear****	3.43wt%	5.63mg
	sodium chloride	1.15wt%	1.88mg
25	**** mixture containing hydroxypropyl methyl cellulose and polyethylene glycol		

Inner Coating: None

Outer Coating:

30	cellulose acetate	1.96wt%	3.21mg
	Eudragit S 100 <sup>1</sup>	0.66wt%	1.09mg
	acetyl tributyl citrate	0.32wt%	0.52mg
	sugar, confectioners 6X micronized	0.98wt%	1.61mg
35		100.00wt%	163.99mg

Coated tablets were prepared using the general procedure of Example 3 except that no inner coating was

applied and an outer enteric coating was applied as an overcoat over the outer layer.

A comparison of Examples 2, 3 and 4 shows that the following was the weight of the coatings that were applied:

Example 2    Inner Coating 4wt%  
              Outer Coating 2wt%  
              Over Coating 0%

Example 3    Inner Coating 0%  
              Outer Coating 3wt%  
              Over Coating 2.5%

Example 4    Inner Coating 0wt%  
              Outer Coating 4wt%  
              Over Coating 0wt%

It is believed that administration of the above described micronized Lovastatin in these amounts will be particularly effective in inhibiting the biosynthesis of cholesterol in the liver through interruption of HMG coenzyme A reductase. The dosage of lovastatin should be individualized depending on the desired and/or degree of serum cholesterol that is desired. Generally 10 to 80mg of lovastatin per day should be administered by mouth depending on the response and the degree of reduction in serum cholesterol level that is indicated.

The foregoing description of a preferred embodiment of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention precise form disclosed. Obvious modifications or variations are possible in light of the above teachings. All such obvious modifications and variations are intended to be within the scope of the appended claims.

We Claim:

1. A controlled release dosage formulation containing an alkyl ester of a substituted naphthalene compound, said formulation comprising:
  - (a) a compressed tablet core which contains an alkyl ester of a substituted naphthalene compound, a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and
  - (b) an outer coating layer which completely covers the osmotic core and comprises a pH sensitive coating agent and a water insoluble polymer.
2. A controlled release formulation as defined in claim 1 wherein the alkyl ester of a hydroxy substituted naphthalene compound is selected from the group consisting of mevastatin, pravastatin, simvastatin and lovastatin.
3. A controlled release dosage form as defined in Claim 2 wherein said compressed tablet core is provided with a first coating to seal the tablet core.
4. A controlled release dosage form as defined in Claim 2 wherein said compressed tablet core is provided with an inner enteric coating.
5. A controlled release dosage form as defined in Claim 2 wherein said compressed tablet core is provided with an overcoat which is an enteric coating.
6. A controlled release dosage form as defined in Claim 2 wherein the pharmaceutically acceptable water swellable polymer is polyethylene oxide.
7. A controlled release dosage form as defined in Claim 2 wherein the osmotic agent is anhydrous lactose.

8. A controlled release dosage form as defined in Claim 2 wherein the pH sensitive coating agent is a copolymer of poly(methacrylic acid and methylmethacrylate.

5

9. A controlled release dosage form as defined in Claim 2 wherein the tablet core contains a surface active agent.

10

10. A controlled release dosage form as defined in Claim 2 wherein the tablet core contains sodium lauryl sulfate.

15

11. A controlled release dosage form which comprises:  
(a) a compressed tablet core which comprises lovastatin, a polyoxyethylene water swellable polymer and anhydrous lactose;

20

(b) an outer coating layer which comprises a mixture of a copolymer of poly(methacrylic acid/methylmethacrylate and a cellulose acetate polymer at a weight ratio of 0.1:1 to 0.75:1.

25

12. A controlled release dosage formulation which comprises:

(a) a compressed tablet core comprising lovastatin, a pharmaceutically acceptable, water swellable polymer and an osmotic agent;

(b) an inner coating layer which comprises a pH sensitive coating agent; and

30

(c) an outer coating layer which comprises a pH sensitive coating agent and a water insoluble polymer.



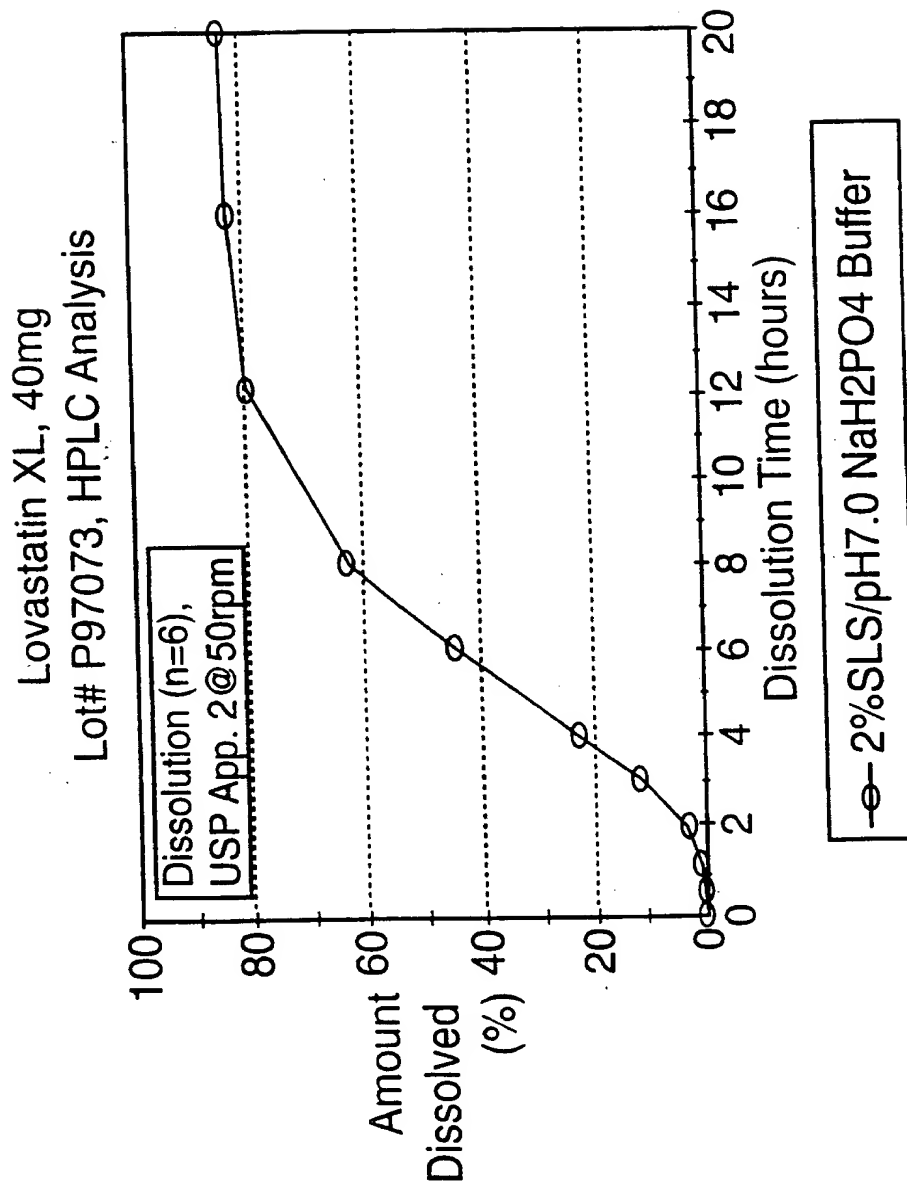


FIG. 1

2/3

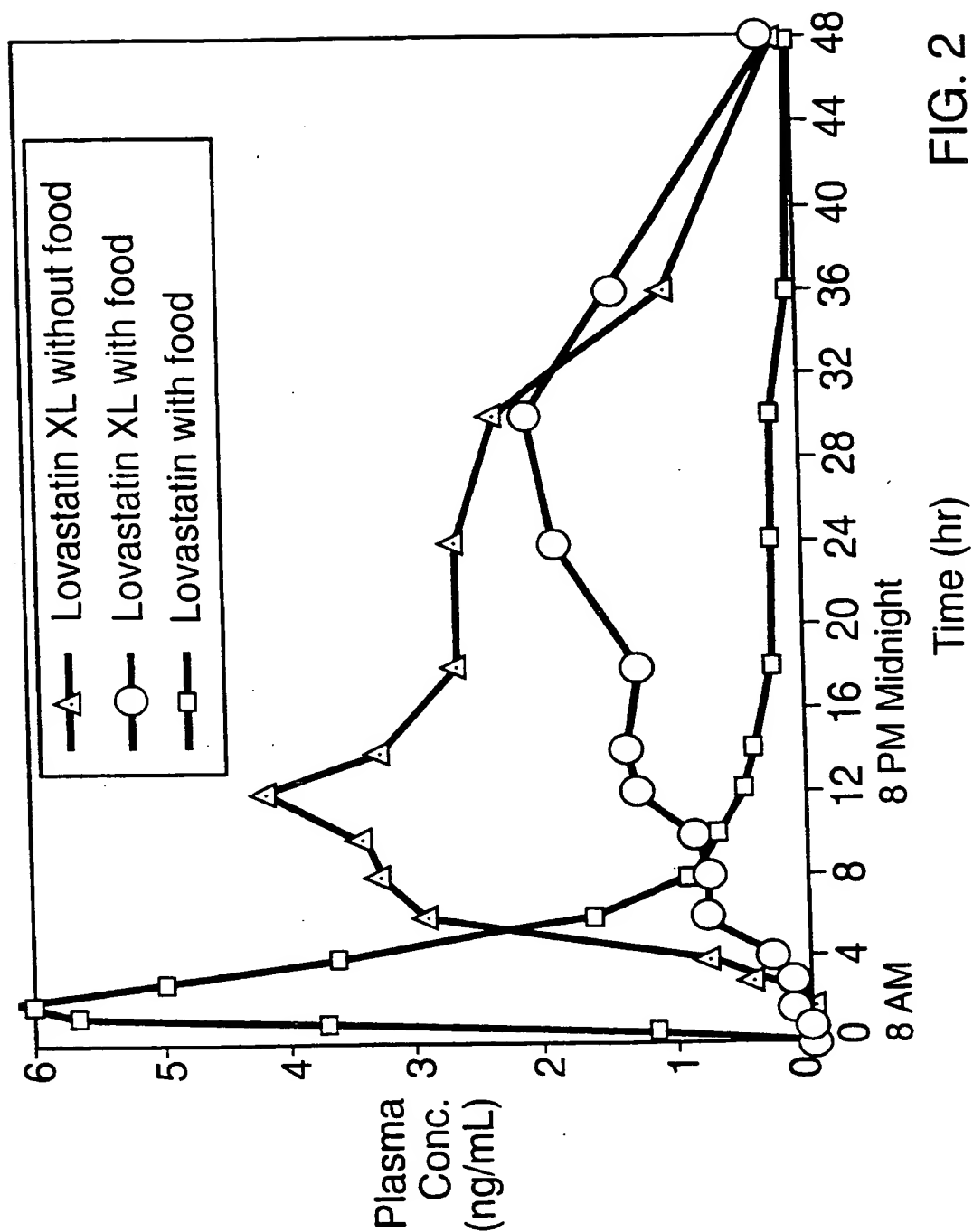


FIG. 2

3/3

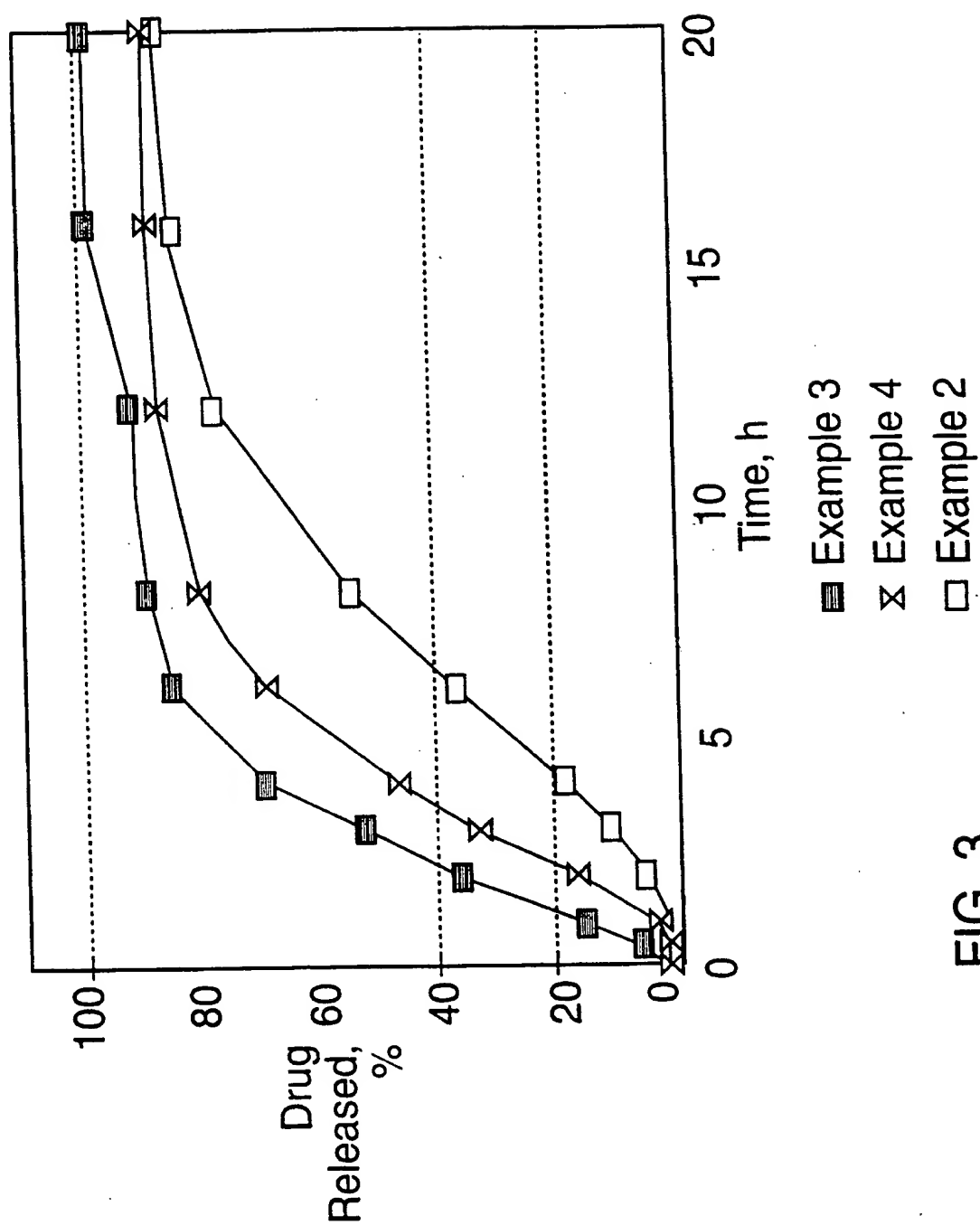


FIG. 3

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/25766

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 9/36

US CL : 514/529; 424/480

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/529; 424/480

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,543,154 A (RORK et al.) 06 August 1996.	1-12
A	US 5,366,738 A (RORK et al.) 22 November 1994.	1-12
A	US 5,582,838 A (RORK et al.) 10 December 1996.	1-12
A	US 5,616,593 A (PATEL et al.) 01 April 1997.	1-12
A	US 5,244,916 A (BOKOCH) 14 September 1993.	1-12

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 JANUARY 1999

Date of mailing of the international search report

01 FEB 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MICHAEL A. WILLIAMSON

Telephone No. (703) 308-1235